

Sobi

Emapalumab/Anakinra

Clinical Study No: Sobi.IMMUNO-101

A phase 2/3, randomized, open-label, parallel group, 3-arm, multicenter study investigating the efficacy and safety of intravenous administrations of emapalumab, an anti-interferon gamma (anti-IFN γ) monoclonal antibody, and anakinra, an interleukin-1(IL-1) receptor antagonist, versus standard of care, in reducing hyper-inflammation and respiratory distress in patients with SARS-CoV-2 infection.

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Sponsor's Medical Director

Cristina de Min, MD
Senior Advisor
Messeplatz 10, 4058 Basel, Switzerland
Telephone No: +41 79 525 14 59
E-mail: Cristina.DeMin@sobi.com

DocuSigned by:
Cristina de Min
Signer Name: Cristina de Min
Signing Reason: I approve this document
Signing Time: 01 July 2020 | 10:49:19 CEST

22694E09A24446E6A381418D2BE9259B
Signature

Date

Principal Coordinating Investigator

Dr. Emanuele Nicastrì, MD
Direttore Dipartimento di Malattie Infettive ad alta
Intensità di cura ed altamente contagiose
Istituto Nazionale per le Malattie Infettive, Ospedale
Lazzaro Spallanzani Via Portuense 292, 00149 Rome,
Italy
E-mail: Emanuele.Nicastrì@inmi.it

Signature

Date

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Investigator statement

I have read the protocol entitled “A phase 2/3, randomized, open-label, parallel group, 3-arm, multicenter study investigating the efficacy and safety of intravenous administrations of emapalumab, an anti-interferon gamma (anti-IFN γ) monoclonal antibody, and anakinra, an interleukin-1 (IL-1) receptor antagonist, versus standard of care, in reducing hyper-inflammation and respiratory distress in patients with SARS-CoV-2 infection.” and the accompanying current Investigator’s Brochure for emapalumab and Summary of Product Characteristics for anakinra. I agree to conduct the clinical investigation in compliance with the Final Protocol Version 7.0, 24 June 2020, the International Council for Harmonisation (ICH) harmonised guideline E6(R2): Guideline for Good Clinical Practice (GCP) [1], applicable regulatory/government regulations, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki [2]. It should be noted that due to the urgency of the situation, the Sponsor has for this protocol requested exemptions to what is required for a Clinical Trial Application and when conducting a clinical trial.

I will not implement any changes to study procedures or conduct without prior approval from the Sponsor and, when applicable, the Independent Ethics Committee and Regulatory Authority. I will supervise any individual or party to whom I delegate study-related duties and functions conducted at the study site and ensure qualification of individuals or parties who perform delegated tasks.

I agree to maintain the confidentiality of this study protocol, as described on the title page. Further, I will not publish results of the study without authorization from Swedish Orphan Biovitrum AB.

Signature of Principal Investigator

Date

Printed Name of Principal Investigator

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Synopsis

STUDY IDENTIFIERS

Title of study:	A phase 2/3, randomized, open-label, parallel group, 3-arm, multicenter study investigating the efficacy and safety of intravenous administrations of emapalumab, an anti-interferon gamma (anti-IFN γ) monoclonal antibody, and anakinra, an interleukin-1(IL-1) receptor antagonist, versus standard of care, in reducing hyper-inflammation and respiratory distress in patients with SARS-CoV-2 infection.
Clinical study number:	Sobi.IMMUNO-101
Sponsor	Swedish Orphan Biovitrum AB, Stockholm, Sweden
Study sites	International multi-center study, 12 to 20 sites in Italy and US are planned to participate in the study.
Type of study:	Phase 2/3

STUDY RATIONALE

As shown by the data available in the most recent literature generated from the Chinese experience, and by the most recent data made available by the different Italian hospitals responsible for the management of these patients, hyper-inflammation, caused by a cytokine storm resulting from an exaggerated response of the immune system to the presence of the virus, is considered to represent one of the most important negative prognostic factor in patients infected with SARS-CoV-2. The inclusion criteria for hyperinflammation used in this protocol is based on the analysis of routine blood chemistry data obtained from patients with SARS-CoV-2 infection. This criterion has been designed with high sensitivity (>90%) for patients who require ICU admission. This constitute the rationale for testing drugs specifically targeted to reduce the cytokine storm.

This protocol has been prepared on the basis to address the current medical emergency, given the severity of the disease and the extremely high number of individuals affected. The objective of this study is to investigate new possibilities to reduce the number of patients requiring mechanical ventilation. This is intended to address the most urgent need to preserve the access to intense care unit support to the lower possible number of patients and may potentially reduce mortality.

STUDY OBJECTIVES

Primary objective:	The primary objective of this study is to assess the effect of emapalumab and anakinra on hyperinflammation and pulmonary function in patients with SARS-CoV-2 infection.
Secondary objective(s):	The secondary objective of this study is to evaluate the safety and tolerability profile, including evaluation of the immunogenicity of emapalumab and anakinra, of intravenous (i.v.) administrations of emapalumab and anakinra in patients with SARS-CoV-2 infection.
Exploratory objective(s):	<p>An exploratory objective of this study is to evaluate the clinical status based on a 7-point ordinal scale.</p> <p>An exploratory objective of this study is to evaluate the PK of emapalumab and anakinra.</p> <p>An exploratory objective of this study is to assess the effect of anakinra and emapalumab on CXCL9, IFNγ, IL-1, IL-6, sIL-2R and selected biomarkers relevant for hyperinflammation.</p>

STUDY ENDPOINTS

Primary endpoint:

The primary endpoint is treatment success, defined as not requiring any of the following by Day 15:

Secondary endpoints supporting the primary objective:

1. Invasive mechanical ventilation or
2. Extracorporeal membrane oxygenation (ECMO).
1. Time to mechanical ventilation.
2. Change from baseline in MEWs score.
3. Change from baseline in resting SpO₂.
4. Change from baseline in PaO₂/FiO₂.
5. Change from baseline in hemogasanalysis.
6. Change from baseline in oxygen supplementation.
7. Amelioration of the findings of high-resolution CT scan or X-ray of the chest.
8. Change from baseline in hyperinflammatory parameters during treatment until Day 15 with measurements performed every 3 days:
 - Ferritin
 - LDH
 - D-dimers
9. Change from baseline in other relevant laboratory parameters during treatment until Day 15 with measurements performed every 3 days:
 - WBC with differential counts
 - RBC
 - Hb
 - Platelet count
 - Fibrinogen
 - Complement C3/C4
 - Prothrombin time
 - Cardiac troponin
 - Liver tests (AST, ALT, total bilirubin levels)
 - CRP
 - Creatinine
 - Electrolytes (Sodium, Potassium and Calcium)
 - Glucose
10. Overall survival.
11. Time to hospital discharge.

Secondary endpoint

Safety endpoints of this study are:

1. Treatment-emergent serious adverse events (SAEs).
2. Adverse events leading to premature discontinuation of study treatment.
3. Infusion related reactions including anaphylactic/anaphylactoid reactions.
4. Treatment emergent adverse events of special interest.
5. Emapalumab treatment group: All new infections. Anakinra treatment group: Severe neutropenia. Treatment-emergent laboratory abnormalities.
6. Presence of anti-drug antibodies (ADAs) and neutralizing antibodies (Nabs) against emapalumab and anakinra.

Exploratory endpoint(s):

Clinical status based on a 7-point ordinal scale.

The scale consists of the the following categories:

1. Death
2. Hospitalized, requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
3. Hospitalized, requiring non-invasive ventilation or high flow oxygen devices
4. Hospitalized, requiring supplemental oxygen
5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care
6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care
7. Not hospitalized

PK parameters will be calculated for emapalumab and anakinra by non-compartmental analysis and population analysis, as applicable.

PD biomarkers: Change from baseline in CXCL9, IFN γ , IL-1, IL-6, sIL-2R and selected biomarkers relevant for hyperinflammation.

STUDY DESIGN AND METHODS

Study design:	<p>This is a randomized, open-label, parallel group, 3-arm multicenter study to investigate the efficacy and safety of emapalumab and anakinra in reducing hyper-inflammation and respiratory distress in adult patients with a documented SARS-CoV-2 infection.</p> <p>The study consists of screening, a 2-week treatment period and an 8-week follow-up period.</p> <p>The 2-week treatment period is open, and the patients will be randomized to treatment with emapalumab, anakinra or standard of care in a 1:1:1 ratio. Emapalumab will be administered as i.v. infusions every 3rd day for a total of 5 infusions (Days 1, 4, 7, 10, 13). Anakinra will be administered as 4-times daily i.v. infusions for 15 days (Days 1 to 15). The primary endpoint will be evaluated at Day 15.</p> <p>An early follow-up visit will be performed at Day 28. A follow-up by visit or phone call will be performed 4 and 8 weeks after the end of the treatment period (Weeks 6 and 10).</p> <p>The study duration for an individual patient will not exceed 10 weeks. The end of the study is defined as last patient last follow-up visit/phone call.</p> <p>The study design has a total sample size of 54 patients and consists of two stages. At the end of Stage 1, the success rates are compared between each of the two treatment arms and standard of care and there is the potential to stop for futility. A data review committee composed of independent experts in intensive care, inflammation, infection diseases will be involved in study oversight, safety monitoring and interpretation of the study results.</p> <p>A safety review committee consisting of internal Sobi members (voting) and coordinating investigators (non-voting) members is established to monitor study participant safety in the study. Clinical safety information will be monitored and reviewed on a continuous basis by the SRC from study start to database lock. Should two patients develop a life threatening or fatal adverse event suspected to be study drug related then an ad hoc SRC meeting will be held within 24 hours after the Sponsor awareness of the event. The SRC has the possibility to take a decision to halt the enrolment of a specific study arm or continue the study with or without changes. Details are described in separate written operating procedures for the SRC.</p> <p>In patients showing worsening of clinical condition, independently of the treatment arm, the Investigator is completely free to decide to introduce any drug considered necessary for a given patient as rescue treatment.</p>
Number of subjects planned:	The study will enroll a total of 54 patients, 18 per arm according to the 1:1:1 randomization.
Diagnosis and main criteria for inclusion:	Patients with documented SARS-CoV-2 infection, age > 18 to < 85 years with respiratory distress and hyperinflammation.

Assessments: The clinical and laboratory parameters to be collected at given time points are indicated in the simplified Schedule of Events presented in the end of the synopsis. This schedule also includes information on the patient's demographics, medical history and prior medication.

Test product; dose and mode and duration of administration: The patients will receive investigational medicinal products (IMP) according to the randomization schedule and table below.

Arm	IMP	Route	Daily dose	Dosage regimen
A	Ema-palumab	i.v. infusion	Day 1: 6 mg/kg Days 4, 7, 10, 13: 3 mg/kg	Every 3 rd day for in total 5 infusions
B	Ana-kinra	i.v. infusion	Days 1-15: 400 mg/day in total, divided into 4 doses given every 6 hours	4 times daily for 15 days
C	None	N/A	N/A	N/A

Prophylactic Therapy: For patients randomized to emapalumab, prophylaxis for Herpes Zoster virus infection has to be in place from the day before initiation of emapalumab treatment until end of study

Concomitant Therapy: Concomitant use of IL-6 inhibitors (e.g., tocilizumab), non-anakinra IL-1 inhibitors (e.g. canakinumab), TNF inhibitors and JAK inhibitors is not allowed. If any of these therapies are initiated at the discretion of the Investigator e.g., as rescue therapy due to worsening of the patient's condition, then the patient should be withdrawn from study.

Hydroxychloroquine, chloroquine, glucocorticoid treatment, antimicrobial therapy and prophylaxis are not limited.

Analgesic treatment, transfusion of blood products, electrolyte and glucose infusions, i.v. parenteral nutrition, positive inotropic support, antibiotics, anti-fungal and anti-viral treatments (e.g. remdesivir), ultrafiltration or hemodialysis, as well as general supportive care are permitted.

Determination of sample size: The study will enroll a total of 54 patients, 18 per arm according to the 1:1:1 randomization. Patients will be stratified based on glucocorticoid treatment at randomization to ensure an equal distribution between treatment arms.

The sample size has been estimated based on the following assumptions:

1. An overall one-sided significance level for efficacy of 0.097 (9.7%) and a power of 74% for each comparison under the assumption that the true success rates are 50% in the SoC group increasing to 80% in the emapalumab or anakinra groups.
2. The study will consist of two stages, with equal numbers of patients randomised into Stage 1 and into Stage 2 per treatment arm.
3. There is the potential to stop for futility of emapalumab or anakinra (or both) at the end of Stage 1.
4. The futility rule for stopping at the end of Stage 1 is binding.

More specifically:

1. The emapalumab or anakinra arm (or both) will be stopped at the end of Stage 1 for futility if the one-sided p-value in favour of emapalumab/anakinra is > 0.690 .
2. The emapalumab or anakinra arm (or both) will be stopped for efficacy at the end of Stage 1 if the one-sided p-value in favour of emapalumab/anakinra is < 0.025 .

If the trial continues to Stage 2, efficacy will be declared at the end of Stage 2 if the one-sided p-value in favour of emapalumab/anakinra is < 0.159 .

Statistical methods:

For the analysis of the primary endpoint, each of the pairwise comparisons, emapalumab/anakinra versus standard of care, at both the end of Stage 1 and at the end of Stage 2, will be undertaken using Fishers Exact test comparing the proportion of patients with treatment success. The p-value calculations will be supplemented by the presentation of one-sided exact confidence intervals. A sensitivity analysis of the primary endpoint will also be conducted, using exact logistic regression adjusting for the stratification factor concurrent glucocorticoid treatment.

Analysis of the time to mechanical ventilation, overall survival, and time to hospital discharge, respectively, will be undertaken by plotting Kaplan-Meier curves for each of the 3 treatment groups and by pairwise comparisons (emapalumab/anakinra versus standard of care) using the logrank test. Hazard ratios will be estimated using the Cox proportional hazards model and these will be presented together with 90% two-sided confidence intervals.

Change from baseline in MEWs score at Day 15 will be analysed using analysis of covariance (ANCOVA) including treatment arm as a fixed factor and baseline MEWs score as a covariate. Least square mean change per group, associated 90% two-sided CI, and p-values for the comparison vs. standard of care, will be presented.

All efficacy analyses will be conducted on the modified intention-to-treat (mITT) population which will comprise all randomized patients except patients who did not receive study treatment or patients who tested negative to SARS-CoV-2 diagnosis by PCR testing.

Schedule of Event (for a detailed version, please refer to Section 5.5.1.1)										
ASSESSMENT	SCREENING	TREATMENT PERIOD						Early follow-up	FOLLOW-UP PERIOD	
	Up to 72h prior to Visit 1	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8/TC	Visit 9/TC
		Day 1 (Baseline)	Day 4	Day 7	Day 10	Day 13	Day 15 (± 1 day)	Day 28 (± 3 day)	Week 6 (± 5 days)	Week 10 (± 5 days)
Informed consent	X									
Eligibility criteria	X	X								
TB screening	X									
PCR SARS-CoV-2	X									
Patient information	X									
Symptom onset information	X									
Physical examination	X									
Vital signs assessment	X	X	X	X	X	X	X	X		
ECG assessment	X						X	X		
HRCT scan or X-ray of chest	X						X	X		
Laboratory assessments (local)	X	X	X	X	X	X	X	X		
Urine pregnancy test	X						X			
Randomization		X								
IMP administration		X-----X								
Concomitant medication incl background therapy		X	X	X	X	X	X	X		
Pulmonary function		X	X	X	X	X	X	X		
PaO ₂ /FiO ₂	X						X	X		
Resting SpO ₂ (3 times per day)		X	X	X	X	X	X	X		
Hemogasanalysis		X	X	X	X	X	X	X		
Oxygen supplementation		X	X	X	X	X	X	X		
MEWS score		X					X	X		
Survival								X	X	X
Time to hospital discharge								X	X	X
Clinical status 7 point ordinal scale		X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X
Biomarkers		X	X	X	X	X	X	X	X	X

Schedule of Event (for a detailed version, please refer to Section 5.5.1.1)										
ASSESSMENT	SCREENING	TREATMENT PERIOD						Early follow-up	FOLLOW-UP PERIOD	
	Up to 72h prior to Visit 1	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8/TC	Visit 9/TC
		Day 1 (Baseline)	Day 4	Day 7	Day 10	Day 13	Day 15 (± 1 day)	Day 28 (± 3 day)	Week 6 (± 5 days)	Week 10 (± 5 days)
PK: emapalumab/anakinra serum concentration		X	X	X	X	X	X	X	X	X
Immunogenicity		X					X	X	X	X
Viral shedding		X			X		X	X	X	X

Abbreviations: CPAP, continuous positive airway pressure; ECMO, extracorporeal membrane oxygenation; FiO₂, fraction of inspired oxygen; HRCT, high resolution computed tomography; IMP, Investigational Medicinal Product; MEWS, modified early warning system; PaO₂, partial pressure of oxygen; SpO₂, peripheral capillary oxygen saturation

1 Abbreviations and definition of terms

1.1 List of abbreviations and definitions

Term	Definition
ADA	Anti-drug antibodies
AE	Adverse event
AIFA	The Italian national competent authority
AOSD	Adult onset Still's disease
AST	aspartate aminotransferase
ALT	Alanine aminotransferase
Baseline	Before study drug administration at Visit 1 (Day 1)
CAPS	Cryopyrin-associated periodic syndrome
CDASH	Clinical data acquisition standards harmonization
CDISC	Clinical data interchange standards consortium
CPAP	Continuous positive airway pressure
CRO	Contract research organization
CRF	Case report form
CRP	C-reactive protein
CT	Computed tomography
CXCL9	Chemokine (C-X-C Motif) ligand 9
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
FiO ₂	Fraction of inspired oxygen
GCP	Good clinical practice
Hb	Hemoglobin
HLH	hemophagocytic lymphohistiocytosis
pHLH	Primary hemophagocytic lymphohistiocytosis
sHLH	Secondary hemophagocytic lymphohistiocytosis
ICH	International council for harmonisation

IEC	Independent ethics committee
IL	Interleukin
IL-1Ra	Interleukin 1 receptor antagonist
IMP	Investigational medicinal product
IFN γ	Inteferon gamma
IRB	Institutional review board
IRS	Interactive response system
i.v.	Intravenous
LDH	Lactate dehydrogenase
MAS	Macrophage activation syndrome
MedDRA	Medical dictionary for regulatory activities
MEW score	The modified early warning score
Nab	Neutralizing antibodies
NOMID	Neonatal-onset multisystem inflammatory disease
NYHA	New York heart association
PaO ₂	Partial pressure of oxygen
PLT	Platelets
RA	Rheumatoid arthritis
PCR	Polymerase chain reaction
PK	Pharmacokinetic
RBC	Red blood cells
RR	Respiratory rate
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
s.c.	Subcutaneous
SJIA	Systemic juvenile idiopathic arthritis
Sobi	Swedish Orphan Biovitrum AB (publ)
SoC	Standard of care
SOP	Standard operating procedure
SpO ₂	Peripheral capillary oxygen saturation

SRC	Safety review committee
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TNF	Tumor necrosis factor
WBC	White blood cells

2 Ethics

2.1 Independent ethics committee and institutional review board

It is the responsibility of the investigator to obtain approval of the study protocol, possible amendments and the written subject information and informed consent form from the IEC/IRB. The investigator should file all correspondence with the IEC/IRB. Copies of IEC/IRB correspondence and approvals should be forwarded to Swedish Orphan Biovitrum (Sobi) or to the CRO as applicable.

2.2 Ethical conduct of the study

This study will be conducted in compliance with this protocol, the ICH GCP [1], applicable regulatory requirements, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki) [2].

It should be noted that due to the urgency of the situation the Sponsor has for this protocol requested and been granted certain exemptions in connection to the approval in Italy to what is required for a Clinical Trial Application, certain ICH GCP requirements and when conducting a clinical trial (see Appendix 3). A study exemption to AE reporting is included in the study protocol in order to minimize clinical burden during the SARS-CoV-2 pandemic, limiting reporting to SAEs, AEs leading to premature discontinuation of study treatment, and AEs of special interest as described in the protocol (Section 5.5.4.3.1).

2.3 Patient information and consent

It is the responsibility of the investigator to give each patient (or the patient's acceptable representative) prior to any study-related activities, full and adequate verbal and written information regarding the objective and procedures of the study and the possible risks involved. The patients must be informed about their right to withdraw from the study at any time. The written patient information and/or informed consent form must not be changed without prior discussion with Sobi. Before any revisions are implemented, the revised written patient information and/or informed consent form must be approved by the IEC/IRB.

It is the responsibility of the investigator to obtain signed informed consent (or witnessed verbal consent according to applicable regulations) from all patients prior to any study-related activities. The patients should receive a copy of the written information and the signed informed consent form.

3 Introduction

3.1 Background

This protocol has been prepared in response to the request formulated by Prof. Franco Locatelli (current President of the Italian Consiglio Superiore di Sanità and member of the Scientific Committee of the Italian Civil Protection, previously serving as Principal Investigator for the European development of emapalumab in children with primary HLH), and the Scientific Director of the National Institute for Infectious Diseases (INMI) Lazzaro Spallanzani, Prof. Giuseppe Ippolito. INMI is the only IRCCS (national institute for research and care of the Italian Ministry of Health) fully devoted to Infectious disease and as WHO-CC for diagnosis, research, care and training against highly infectious diseases. Both are members of the Scientific Committee of the Italian Civil Protection and are working in strict collaboration with the Italian national competent authority (AIFA) and are committed to investigate, among others, the use of emapalumab and anakinra, in patients suffering from the SARS-CoV-2 infection and experiencing respiratory distress.

For the preparation of this protocol, expertise in hyperinflammation, in the treatment of cytokine release syndromes, and in the treatment of infectious diseases, has been provided by Franco Locatelli, Fabrizio De Benedetti and Giuseppe Ippolito, together with contribution of the many physicians currently involved in the treatment of patients infected with SARS-CoV-2 in Italy.

Following discussions with the FDA and given the global urgency to develop treatment for patients with SARS-CoV-2 infection and experiencing respiratory distress, the study protocol has been amended to include US study sites and patients. The current study is intended to provide proof of concept for the treatment of anakinra and/or emapalumab as add-on to standard of care, and to guide the plan for further development.

The objective of this study is to investigate new possibilities to reduce the number of patients requiring mechanical ventilation. This is intended to address the most urgent need to preserve the access to intense care unit support to the lower possible number of patients and may potentially reduce mortality.

3.2 Study rationale

As shown by the data available in the most recent literature generated from the Chinese experience [4, 5, and 6], and by the most recent data made available by the different Italian hospitals responsible for the management of these patients (unpublished data generated in the laboratory of Immunology of the National Institute for Infectious Diseases and the Laboratory of ImmunoRheumatology of the Ospedale Pediatrico Bambino Gesù), hyper-inflammation, caused by a cytokine storm resulting from an exaggerated response of the immune system to the presence of the virus, is considered to represent one of the most important negative prognostic factor in patients infected with SARS-CoV-2. The inclusion criteria for hyperinflammation used in this protocol is based on the analysis of routine blood chemistry data obtained from patients with SARS-CoV-2 infection. This criterion has been designed with high sensitivity (>90%) for

patients who require ICU admission. This constitute the rationale for testing drugs specifically targeted to reduce the cytokine storm.

3.3 Potential risks and benefits

Anakinra is a recombinant form of the human IL-1Ra, r-metHuIL-1Ra, which is produced by recombinant DNA technology in an E. coli expression system. Therapeutically, anakinra neutralizes the biological activity of IL-1 (IL-1 α and IL-1 β) by competitively inhibiting its binding to the IL-1RI.

Kineret (anakinra) was first approved for treatment of RA in the US in 2001 and subsequently in the EU/EEA in 2002. More than 3000 patients were included in this development program.

In 2012, an sBLA on anakinra for treatment of NOMID was approved in the US. Kineret is also approved for treatment of CAPS (in EU/EEA, Israel and Australia), Still's disease, including SJIA and AOSD (in EU/EEA), FMF (in EU/EEA), and SJIA (in Australia).

The initial IND for anakinra was granted in 1991. The estimated cumulative exposure to anakinra in completed company sponsored clinical studies up to 1 May 2018 is 6404 subject-years in 8518 subjects with various indications.

Anakinra is administered s.c. at doses of 100 mg/day (RA) or in weight-based doses of up to 8 mg/kg/day (NOMID). In clinical studies in sepsis, doses up to 2 mg/kg/hour i.v. over 72 hours were administered to >500 patients and were well tolerated. For additional information of i.v. administration of anakinra, see Section 5.4.4.1.

Based on the most recent PSUR (with data from May 1994 through to May 2019) the estimated exposure to anakinra in completed company sponsored clinical studies is 6404 subject-years in 8518 subjects. The cumulative post-marketing exposure is estimated to 113 414 patient years.

The safety profile of anakinra has been consistent across indications, age groups, and doses studied; this includes data that have been reported in the literature for off-label indications. The safety profile has remained stable also when anakinra has been studied in long-term safety studies and in patients with various co-morbidities. There are no indications of increasing AE rates over time. The most common AEs are non-serious, mostly mild to moderate injection site reaction that usually occur early and resolve during continued anakinra treatment. No dose-limiting toxicities have been observed in clinical studies or during post-marketing use and the maximum tolerated dose has not been established. There are no indications of changes to the safety profile even when very high doses are administered.

For the most recent information about anakinra, please refer to the current Summary of Product Characteristics (SPC).

Emapalumab (previously referred to as NI-0501, trade name Gamifant®) is a fully human Immunoglobulin G1 (IgG1) Anti-Interferon gamma (IFN γ) monoclonal antibody that binds to and neutralizes IFN γ .

Emapalumab binds to both soluble and receptor (IFN γ R1)-bound forms of IFN γ .

Emapalumab is in development for the treatment of primary and secondary forms of HLH. The benefit expected from the targeted neutralization of IFN γ by emapalumab has been validated by the FDA approval in November 2018 of emapalumab for the treatment of patients with primary HLH who have refractory, recurrent or progressive disease or intolerance with conventional HLH therapy. The safety profile of emapalumab has been assessed as acceptable, and no post-marketing commitments have been requested by the FDA with regard to safety.

Since the start of the clinical development program for emapalumab, 103 patients have received emapalumab in clinical trials and through compassionate use. Furthermore, 70 patients have been treated to date in the US following FDA approval, and post-marketing surveillance has not revealed any additional safety concerns with the use of emapalumab.

Based on the analyses conducted to date, no sign of any off-target effect of emapalumab has been detected.

Multiple medications have been administered concomitantly with emapalumab and no evidence of significant drug-drug interactions has been reported so far.

For the most recent information about emapalumab, please refer to the current Investigator's Brochure (version 10.0, dated 24 JAN 2020).

The overall assessment is that the benefit of using anakinra and emapalumab as add-on to standard of care in patients diagnosed with SARS-CoV-2 infection outweighs the risks.

4 Study objectives and endpoints

4.1 Primary objective

The primary objective of this study is to assess the effect of emapalumab and anakinra on hyperinflammation and pulmonary function in patients with SARS-CoV-2 infection.

4.1.1 Primary endpoint

The primary endpoint is treatment success, defined as not requiring any of the following by Day 15:

- Invasive mechanical ventilation or
- Extracorporeal membrane oxygenation (ECMO).

4.1.2 Secondary endpoints supporting the primary objective

- Time to mechanical ventilation.
- Change from baseline in MEWs score.
- Change from baseline in resting SpO₂.
- Change from baseline in PaO₂/FiO₂.

- Change from baseline in hemogasanalysis.
- Change from baseline in oxygen supplementation.
- Amelioration of the findings of high-resolution CT scan or X-ray of the chest.
- Change from baseline in hyperinflammatory parameters during treatment until Day 15 with measurements performed every 3 days:
 - Ferritin
 - LDH
 - D-dimers
- Change from baseline in other relevant laboratory parameters during treatment until Day 15 with measurements performed every 3 days:
 - WBC with differential counts
 - RBC
 - Hb
 - Platelet count
 - Fibrinogen
 - Complement C3/C4
 - Prothrombin time
 - Cardiac troponin
 - Liver tests (AST, ALT, total bilirubin levels)
 - CRP
 - Creatinine
 - Electrolytes (Sodium, Potassium and Calcium)
 - Glucose
- Overall survival.
- Time to hospital discharge.

4.2 Secondary objective

The secondary objective of this study is to evaluate the safety and tolerability profile, including evaluation of the immunogenicity of emapalumab and anakinra, of intravenous (i.v.) administrations of emapalumab and anakinra in patients with SARS-CoV-2 infection.

4.2.1 Secondary endpoints supporting the secondary objective

Safety endpoints of this study are:

- Treatment-emergent serious adverse events (SAEs).
- Adverse events leading to premature discontinuation of study treatment.
- Infusion related reactions including anaphylactic/anaphylactoid reactions.
- Treatment emergent adverse events of special interest:
 - Emapalumab treatment group: All new infections.
 - Anakinra treatment group: Severe neutropenia.
- Treatment-emergent laboratory abnormalities.

- Presence of anti-drug antibodies (ADAs) and neutralizing antibodies (Nabs) against emapalumab and anakinra.
-

4.3 Exploratory objective

An exploratory objective of this study is to evaluate the clinical status based on a 7-point ordinal scale.

An exploratory objective of this study is to evaluate the PK of emapalumab and anakinra.

An exploratory objective of this study is to assess the effect of anakinra and emapalumab on CXCL9, IFN γ , IL-1, IL-6, sIL-2R and selected biomarkers relevant for hyperinflammation.

4.3.1 Exploratory endpoints

Clinical status based on a 7-point ordinal scale.

The scale consists of the the following categories:

1. Death
2. Hospitalized, requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
3. Hospitalized, requiring non-invasive ventilation or high flow oxygen devices
4. Hospitalized, requiring supplemental oxygen
5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care
6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care
7. Not hospitalized

PK parameters will be calculated for emapalumab and anakinra by non-compartmental analysis and population analysis, as applicable.

PD biomarkers: Change from baseline in CXCL9, IFN γ , IL-1, IL-6, sIL-2R and selected biomarkers relevant for hyperinflammation.

5 Investigational plan

5.1 Overall study design and plan

This is a randomized, open-label, parallel group, 3-arm multicenter study to investigate the efficacy and safety of emapalumab and anakinra in reducing hyper-inflammation and respiratory distress in adult patients with a documented SARS-CoV-2 infection.

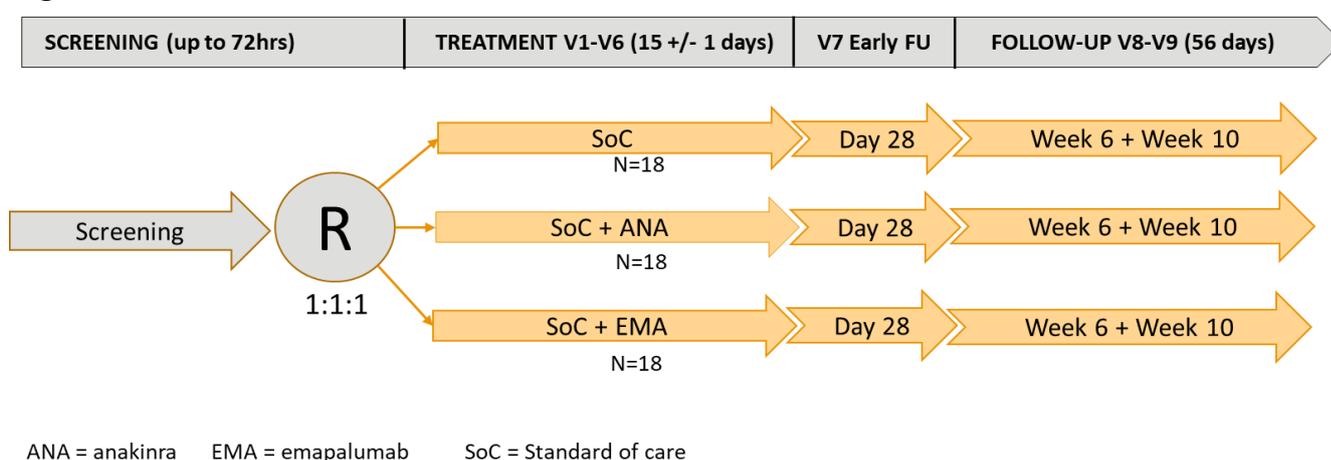
The study consists of screening, a 2-week treatment period and an 8-week follow-up period.

The 2-week treatment period is open, and the patients will be randomized to treatment with emapalumab, anakinra or standard of care in a 1:1:1 ratio. Emapalumab will be administered as i.v. infusions every 3rd day for a total of 5 infusions (Days 1, 4, 7, 10, 13). Anakinra will be administered as 4-times daily i.v. infusions for 15 days (Days 1 to 15). The primary endpoint will be evaluated at Day 15.

An early on-site follow-up visit will be performed at Day 28. A follow-up by visit or phone call will be performed 4 and 8 weeks after the end of the treatment period (Weeks 6 and 10).

The study duration for an individual patient will not exceed 10 weeks. The end of the study is defined as last patient last follow-up visit/phone call.

Figure 1



The study design has a total sample size of 54 patients and consists of two stages. At the end of Stage 1, the success rates are compared between each of the two treatment arms and standard of care and there is the potential to stop for futility.

A data review committee composed of independent experts in intensive care, inflammation, infection diseases will be involved in study oversight, safety monitoring and interpretation of the study results.

A safety review committee consisting of internal Sobi members (voting) and coordinating investigators (non-voting) members is established to monitor study participant safety in the study. Clinical safety information will be monitored and reviewed on a continuous basis by the SRC from study start to database lock. Details are described in a separate written operating procedures for the SRC.

In patients showing worsening of clinical condition, independently of the treatment arm, the Investigator is completely free to decide to introduce any drug considered necessary for a given patient as rescue treatment.

5.2 Discussion of study design, including the choice of control groups

5.3 Selection of study population

5.3.1 Inclusion criteria

A patient must fulfill the following criteria in order to be included in the study:

1. Signed informed consent provided by the patient, or by the patient's legally authorized representative(s), as applicable.
2. Documented presence of SARS-CoV-2 infection as per hospital routine.
3. Age > 18 to < 85 years at the time of screening.
4. Presence of respiratory distress, defined as:
 - a. $\text{PaO}_2/\text{FiO}_2 < 300$ mm Hg and >200 mm Hg **or**
 - b. $\text{RR} \geq 30$ breaths/min **or**
 - c. $\text{SpO}_2 < 93\%$ in air at rest.

Note: Patients given CPAP ventilator support are eligible for inclusion.

5. Presence of hyperinflammation defined as:
 - a. Lymphocyte counts:
 - < 1000 cells/ μL , in patients who have not received systemic glucocorticoids for at least 2 days prior to the assessment of the lymphocyte count
 - < 1200 cells/ μL , in patients who have received systemic glucocorticoids for at least 2 days prior to the assessment of the lymphocyte count
 - and
 - b. One of the following three criteria:
 - i. Ferritin > 500 ng/mL
 - ii. LDH > 300 U/L
 - iii. D-Dimers > 1000 ng/mL

5.3.2 Exclusion criteria

The presence of any of the following will exclude a patient from inclusion in the study:

1. Patients in mechanical ventilation or with MEWS score >4 with evidence of moderate or above ARDS (Berlin definition) or severe respiratory insufficiency or evidence of rapid worsening (respiratory distress requiring mechanical ventilation or presence of shock or presence of concomitant organ failure requiring ICU admission).

Note: For the evaluation of patient eligibility, temperature will not be considered in the calculation of the total MEWS score since presence of fever is a hallmark of SARS-CoV-2 infection.

2. Impairment of cardiac function defined as poorly controlled heart diseases, such as NYHA class II (mild) and above, cardiac insufficiency, unstable angina pectoris, myocardial infarction within 1 year before enrollment, supraventricular or ventricular arrhythmia need treatment or intervention.
3. Severe renal dysfunction (estimated glomerular filtration rate $\leq 30\text{mL}/\text{min}/1.73\text{ m}^2$) or receive continuous renal replacement therapy, hemodialysis, or peritoneal dialysis.
4. Uncontrolled hypertension (seated systolic blood pressure $>180\text{mmHg}$, or diastolic blood pressure $>110\text{mmHg}$).
5. Administration of plasma from convalescent patients who recovered from SARS-CoV-2 infection.
6. Clinical suspicion of active or latent tuberculosis.
7. History of hypersensitivity or allergy to any component of the study drug.
8. Pregnant women.
9. Existence of any life-threatening co-morbidity or any other medical condition which, in the opinion of the investigator, makes the patient unsuitable for inclusion.
10. Enrollment in another concurrent clinical interventional study, or intake of an investigational drug within three months or 5 half-lives prior to inclusion in this study, if considered interfering with this study objectives as assessed by the Investigator.
11. Foreseeable inability to cooperate with given instructions or study procedures.
12. Clinical suspicion of active mycobacteria histoplasma capsulatum, herpes zoster, salmonella and shigella Infections.
13. Patients with liver dysfunction defined as AST or ALT $> 5 \times \text{ULN}$

5.3.3 Withdrawal of patients from treatment or study

5.3.3.1 Withdrawal from treatment

A patient should be withdrawn from the study treatment if, in the opinion of the Investigator, it is medically necessary, or if it is the wish of the patient.

When a patient is withdrawn, the date of last IMP administration and the date and reason for treatment withdrawal should be clearly described in the relevant sections of the CRF. If a patient is removed from treatment because of an AE, the reason for treatment withdrawal should always be stated as 'adverse event' irrespective of whether this was the investigator's or the patient's decision.

The patient will continue to participate in the study without taking study treatment.

5.3.3.2 Withdrawal from study

Whenever possible and irrespective of the reason for withdrawal, the patient should be examined as soon as possible. Relevant samples should be obtained and all relevant assessments should be completed, preferably according to the schedule for Visit 6 (Day 15). The CRF should be completed as far as possible. Date and reason for the study withdrawal should be clearly described in the CRF.

5.3.4 Replacement of withdrawn patients

Patients withdrawn from the study will not be replaced.

5.3.5 Screening failures

Screening failures are defined as patients who consent to participate in the study but are not subsequently randomized into the study. A minimal set of screening failure information is required which includes demographics, reason for screen failure and failed eligibility criteria.

Patients who do not meet the criteria for participation in this study (screening failure) may not be rescreened.

5.4 Treatments

5.4.1 Treatments administered

The patients will receive investigational medicinal products (IMP) according to the randomization schedule, see Table 1.

Table 1 Investigational medicinal products

Arm	Investigational product	Dosage form	Route	Daily dose	Dosage regimen
A	Emapalumab	Solution	i.v. infusion	Day 1: 6 mg/kg Days 4, 7, 10, 13: 3 mg/kg	Every 3 rd day for in total 5 infusions
B	Anakinra	Solution	i.v. infusion	Days 1-15: 400 mg/day in total, divided into 4 doses given every 6 hours	4 times daily for 15 days
C	None	N/A	N/A	N/A	N/A

5.4.2 Identity of investigational medicinal products

Emapalumab and anakinra will be supplied to the study sites as open-label supplies.

Possible deficiencies related to the handling and quality of the IMPs should be reported to the study monitor and also directly to complaints@sobi.com.

5.4.2.1 Emapalumab

The IMP emapalumab is delivered as a sterile concentrate for infusion, prefilled in single-use glass vials which require a dilution prior to administration. The concentrate of emapalumab in the solution is 5 mg/mL. The solution contains no antimicrobial preservative, and therefore each vial must be used only once.

Emapalumab should be stored between 2 and 8°C (36 and 46°F) in a secure area at the study sites. Further instructions on handling and storage of emapalumab are available in the IMP manual.

Emapalumab is manufactured by a third-party manufacturing facility duly qualified by Sobi AG and is supplied as described in the IMP Manual.

Labeling will comply with national regulatory requirements.

5.4.2.2 Anakinra

The IMP anakinra is delivered as a sterile solution for injection, prefilled in a single-use syringe with the strength 100 mg. The total volume of injection is 0.67 mL and the concentration of anakinra in the solution is 150 mg/mL.

Anakinra must be stored at refrigerated conditions at 2-8 °C (36°-46°F) in a secure area at the study sites. Further instructions for handling and storage of the IMP anakinra are available in the IMP manual.

The anakinra drug substance is manufactured by Boehringer Ingelheim (Vienna, Austria) or by Pfizer (Strängnäs, Sweden) and anakinra drug product is manufactured by Patheon Italia SpA (Monza, Italy).

Labeling will comply with national regulatory requirements.

5.4.3 Method of assigning patients to treatment groups

The different treatment groups are;

- Arm A: Emapalumab as add on to standard of care
- Arm B: Anakinra as add on to standard of care
- Arm C: Standard of care only

The ratio between the treatment groups is 1:1:1, i.e., the same number of patients will be randomized to emapalumab, anakinra, or standard of care. Patients will be stratified based on glucocorticoid treatment at randomization to ensure an equal distribution between treatment arms. The randomization numbers are generated in blocks. Each block includes the three treatment groups per the ratio described above. An IWRS will be used for the randomization.

5.4.4 Selection of doses

5.4.4.1 Dose selection rationale for anakinra

Anakinra is approved for the chronic treatment of a number of inflammatory diseases as a subcutaneous treatment (at doses of 100 mg/day or in weight-based doses of up to 8 mg/kg/day). The i.v. administration of anakinra has been studied in clinical trials in healthy volunteers and in critically ill patients with sepsis and hyper-inflammation at variable i.v. doses up to 3500 mg/day over 72 hours: e.g., 2 mg/kg/hour, 20 mg/kg/day (<40 kg) and 916 mg/day (> 40kg), bolus of 100 mg followed by infusion of 2 mg/kg/hour. No safety concerns emerged in these studies [7, 8, 9, 10, and 11].

A study in children with systemic onset juvenile arthritis complicated by refractory macrophage activation syndrome is currently ongoing (NCT02780583) in which anakinra is administered at dose of 10 mg/kg/day to a maximum of dose of 200 mg/day divided every 12 hours (for children ≤40 kg) or 5 mg/kg/day up to a maximum dose of 400 mg/day divided every 6 hours (children > 40 kg and adults). This dosing schema reflects the dose at which anakinra is administered, although off label, in children affected by this severe disease, as reported in a number of case studies.

Since the start of the current clinical study, there is emerging data based on anakinra given by i.v infusions in treatment of cytokine storm syndromes (21), and emerging data of anakinra i.v administration studied in the SARS-CoV-2 setting (22).

Based on the above, in this study anakinra is administered at a total dose of 400 mg per day, divided in 4 i.v. doses of 100 mg every 6 hours.

5.4.4.2 Dose selection rationale for emapalumab

Preliminary data on inflammatory makers in blood, e.g., D-dimer, LDH and ferritin [4, and unpublished data generated in the laboratory of Immunology of the National Institute for Infectious Diseases and the Laboratory of ImmunoRheumatology of the Ospedale Pediatrico Bambino Gesù] indicate that patients with SARS-CoV-2 infection have longer and more marked inflammatory response. This seems to be more evident in patients with severe disease. These markers, though elevated, appear to be less elevated than what is generally observed in systemic onset Juvenile Idiopathic Arthritis (sJIA) patients who develop Macrophage Activation Syndrome (MAS), a form of secondary HLH. Furthermore, their evolution over time seem to be also less rapid. Of note, it must be mentioned that these observations in blood may not fully reflect the amount of IFN γ released in the inflamed lungs.

The emapalumab dosing scheme used in the ongoing NI-0501-06 study in sJIA/MAS patients (NCT03311854) foresees an initial dose of 6 mg/kg followed by 3 mg/kg every 3 days. The available data in the 9 patients who have completed treatment to date indicate the achievement of complete response in all the patients with no relevant safety or tolerability concern [12]. In the trial in primary HLH, doses up to 10 mg/Kg/infusion have been used again with no relevant safety or tolerability concern [16].

Based on the above, an initial emapalumab dose of 6 mg/kg followed by 3 mg/kg every 3 days has been selected for the present study in SARS-CoV-2 infected patients.

This dose is considered appropriate to give the best chance to demonstrate efficacy in the specific patient population of this study, taking into account (I) the favourable safety profile of emapalumab not only in secondary, but also in primary HLH, (II) the life-threatening condition to be treated, (III) the low number of patients to be enrolled in the study (n=18), (IV) and the extremely challenging situation which the epidemic of SARS-CoV-2 infection represents.

5.4.4.3 Rationale for stratifying the use of glucocorticoids

As glucocorticoids are one of the main first line anti-inflammatory treatments in secondary HLH, they have been suggested as one of the potential treatments for patients with severe SARS-CoV-2 infection [14]. Further to the relevance of the hyper-production of inflammatory cytokines in this infection, initial promising data have been reported with the use of IL-6 targeted therapies, namely tocilizumab, in the treatment of patients with SARS-CoV-2 infection [15]. Noteworthy, in this report all patients treated with tocilizumab also received glucocorticoids.

The use of glucocorticoids in patients with SARS-CoV-2 differs between regions and countries. Based on the experience accumulated so far in Europe, glucocorticoids have become part of standard of care for SARS-CoV-2 patients with hyperinflammation. Meanwhile, in US glucocorticoids currently seem not to be widely used in the treatment of patients with SARS-CoV-2 and hyperinflammation.

Interim WHO guidance argues against the use of glucocorticoids in the treatment of patients with SARS-CoV-2 infection [19]. This view is supported by the Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19 [20].

Glucocorticoids are anti-inflammatory and the potential use of glucocorticoids could have an impact on biomarkers of hyper-inflammation and potentially also on the clinical outcome.

Since the use of glucocorticoids will differ between regions study patients will be stratified based on glucocorticoid treatment at randomization to ensure an equal distribution between treatment arms.

5.4.5 Selection and timing of doses for each patient

5.4.5.1 Emapalumab

Emapalumab will be administered by intravenous (i.v.) infusion over a period of 1 to 2 hours depending on the volume to be infused, at an initial dose of 6 mg/kg.

Emapalumab treatment will be continued at the dose of 3 mg/kg, every 3rd day until Day 13 i.e., Days 4, 7, 10 and 13. The following information will be recorded in the CRF for each emapalumab administration: date, start and end time, total dose infused, and, if infusion was interrupted, reason for interruption.

Emapalumab must be prepared by a Pharmacist or other appropriately qualified staff member, specifically authorized by the Investigator/Pharmacist and appropriately licensed to perform the task.

The specific dose to be administered for an individual infusion will be determined based on the patient's body weight at screening.

Full instructions for the preparation of emapalumab, including dilution steps and method for administration, are available in the IMP manual.

The patient should receive the designated volume of the infusion material through an infusion pump over 1 to 2 hours depending on the volume to infuse. A 0.2 µm filter must be included in all infusion lines.

It is recommended that an i.v. central line remains in place to ensure venous access during the treatment period.

Since no data are available on the compatibility of emapalumab with other i.v. substances or additives, other medications/substances should not be added to the infusion material or infused simultaneously through the same i.v. line. If the same i.v. line is used for subsequent infusions of other drugs, the line should be flushed appropriately with saline before and after infusion of emapalumab.

5.4.5.2 Anakinra

Anakinra will be administered by i.v. infusion at total dose of 400 mg per day, divided in 4 doses 100 mg i.v. every 6 hours.

Anakinra treatment will continue for 15 days i.e., Days 1 to 15. The following information will be recorded in the CRF for each anakinra administration: date, start and end time, total dose infused, and, if infusion was interrupted, reason for interruption.

Before administration, the full content of the prefilled, single-use syringe (anakinra 100 mg) will be diluted in 100 mL saline. The i.v. administration of anakinra has to occur immediately after the preparation over an infusion period of 60 minutes. A particle reduction inline filter will be assembled with the infusion set.

Full instructions for the preparation of anakinra are available in the IMP manual.

5.4.6 Blinding and unblinding

This is an open study with no level of blinding.

5.4.7 Concomitant therapy

5.4.7.1 Prophylactic therapy

For patients randomized to emapalumab, prophylaxis for Herpes Zoster virus infection has to be in place from the day before initiation of emapalumab treatment until end of study.

The prophylactic therapy will be recorded in the CRF.

5.4.7.2 Concomitant therapy

Concomitant use of IL-6 inhibitors (e.g., tocilizumab), non-anakinra IL-1 inhibitors (e.g., canakinumab), TNF inhibitors and JAK inhibitors is **not** allowed. If any of these therapies are initiated at the discretion of the Investigator e.g., as rescue therapy due to worsening of the patient's condition, then the patient should be withdrawn from study (see Section 5.3.3.2).

Hydroxychloroquine, chloroquine, glucocorticoid treatment, antimicrobial therapy and prophylaxis are not limited.

Analgesic treatment, transfusion of blood products, electrolyte and glucose infusions, i.v. parenteral nutrition, positive inotropic support, antibiotics, anti-fungal and anti-viral treatments (e.g., remdesivir), ultrafiltration or hemodialysis, as well as general supportive care are permitted.

Other therapy considered necessary for the patient's welfare may be given at the discretion of the Investigator.

For patients taking other treatments that are substrates for CYP450 with a narrow therapeutic index (e.g. warfarin and phenytoin), the treating physician should make appropriate treatment adjustments and monitor the patient as deemed necessary.

All relevant concomitant therapy, as defined by the Investigator, will be recorded in the CRF.

5.4.8 Treatment compliance

The IMP administrations will be recorded in the CRF as described in Section 5.4.5.

Product accountability records will be kept. The pharmacy and Investigator must maintain accurate records demonstrating date and amount of study drug(s) received, to whom and by whom administered or dispensed (patient-by-patient accounting), and accounts of returned study drug (s) and any study drug accidentally or deliberately destroyed. All unused study drug will be counted.

At the end of the study, any remaining study drug (s) will be destroyed locally or returned to the depot for destruction. In either case, a certificate of destruction must be issued.

5.5 Efficacy and safety assessments

5.5.1 Study schedule

5.5.1.1 Schedule of events

Table 2 Schedule of Events

ASSESSMENT	SCREENING	TREATMENT PERIOD						Early FU	FOLLOW-UP PERIOD	
	Up to 72h prior to Visit 1	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8/TC	Visit 9/TC
		Day 1 (Baseline)	Day 4	Day 7	Day 10	Day 13	Day 15 (± 1 day)	Day 28 (± 3 days)	Week 6 (± 5 days)	Week 10 (± 5 days)
Informed consent	X									
Eligibility criteria	X	X ¹								
TB screening ¹³	X									
PCR SARS-CoV-2 ¹⁴	X									
Patient information ²	X									
Symptom onset information	X									
Physical examination ³	X									
Vital signs assessment ⁴	X	X	X	X	X	X	X	X		
ECG assessment	X						X	X		
HRCT scan or X-ray of chest	X ⁵						X	X		
Laboratory assessments (local) ⁶	X ⁵	X	X	X	X	X	X	X		
Urine pregnancy test ⁷	X						X			
Randomization		X								
IMP administration ⁸		X-----X								
Concomitant medication incl background therapy ⁹		X	X	X	X	X	X	X		
Pulmonary function ¹⁰		X	X	X	X	X	X	X		
PaO ₂ /FiO ₂	X						X	X		
Resting SpO ₂ (3 times per day)		X	X	X	X	X	X	X ¹⁸		
Hemogasanalysis		X	X	X	X	X	X	X		
Oxygen supplementation		X	X	X	X	X	X	X		
MEWS score		X					X	X		
Clinical status 7 point ordinal scale		X	X	X	X	X	X	X	X	X

ASSESSMENT	SCREENING	TREATMENT PERIOD						Early FU	FOLLOW-UP PERIOD	
	Up to 72h prior to Visit 1	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8/TC	Visit 9/TC
		Day 1 (Baseline)	Day 4	Day 7	Day 10	Day 13	Day 15 (± 1 day)	Day 28 (± 3 days)	Week 6 (± 5 days)	Week 10 (± 5 days)
Survival								X	X	X
Time to hospital discharge								X	X	X
Adverse events ¹¹		X	X	X	X	X	X	X	X	X
Biomarkers ¹²		X	X	X	X	X	X	X	X	X
PK: emapalumab/anakinra serum concentration ¹⁵		X	X	X	X	X	X	X	X	X
Immunogenicity ¹⁶		X					X	X	X	X
Viral shedding ¹⁷		X			X		X	X	X	X

Abbreviations: CPAP, continuous positive airway pressure; ECMO, extracorporeal membrane oxygenation; FiO₂, fraction of inspired oxygen; HRCT, high resolution computed tomography; IMP, Investigational Medicinal Product; MEWS, modified early warning system; PaO₂, partial pressure of oxygen; SpO₂, peripheral capillary oxygen saturation. During the treatment period (Days 1 to 15), clinical and laboratory assessments and procedures should preferably be performed before IMP administration.

¹Before study drug administration.

²Includes demographics, medical and surgical history and prior medication.

³Including recording of body weight and length.

⁴Body temperature, blood pressure, heart rate, respiratory rate and oxygen saturation.

⁵HRCT scan results and laboratory results already available in medical records at the time of informed consent can be used to confirm eligibility, if collected within 72 hours.

⁶Ferritin, LDH, D-dimers. WBC with differential counts, RBC, Hb, Platelet count, Fibrinogen, Complement C3/C4, Prothrombin Time, Cardiac troponin, AST, ALT, total bilirubin levels, CRP and Creatinine.

⁷Only applicable for females of childbearing potential.

⁸Emapalumab will be administered once daily Days 1, 4, 7, 10 and 13 (Section 5.4.5.1). Anakinra will be administered 4 times daily for 15 days i.e., Day 1 to 15 (Section 5.4.5.2).

⁹For details, see Section 5.4.7.

¹⁰Requirement for invasive mechanical ventilation or ECMO.

¹¹Incidence, severity, causality and outcomes of treatment-emergent serious AEs, adverse events leading to premature discontinuation of study treatment and adverse events of special interest.

¹²PD biomarkers: CXCL9, IFN γ , IL-1, IL-6, sIL-2R. Samples to be collected Visit 1:pre-dose and thereafter at Visits 2, 3, 4, 5 and 6: end of infusion. (for anakinra treated patients; samples will only be collected in connection with the first infusion per day) In addition, at Visits 8 and 9, a PD biomarker sample will be collected in case the patient is coming to the clinic for these visits.

¹³Local TB testing to confirm patient status. Test result are accepted post randomization not to delay treatment.

¹⁴Local PCR testing to confirm patient SARS-CoV-2 diagnosis. For sites where PCR is not part of hospital routine for confirming diagnosis/eligibility, test results are accepted post randomization not to delay treatment.

¹⁵ PK blood samples will be collected at Visit 1: pre-dose and at end-of infusion (for anakinra after the first infusion per day), and thereafter at Visits 2, 3, 4, 5 and 6: at end-of infusion (for anakinra treated patients; samples will only be collected in connection with the first infusion). In addition, for emapalumab treated patients at Visits 7. For Visit, 8 and Visit 9, a PK sample will be collected in case the patient is coming to the clinic for these visits.

¹⁶ Immunogenicity samples will be collected at Visit 1: Pre-dose and at Visit 6 at end-of infusion (for anakinra after the first infusion per day), and at Visit 7. For Visit 8 and Visit 9 immunogenicity samples will be collected in case the patient is coming to the clinic for these visits.

¹⁷ Viral shedding samples will be collected and stored for subsequent analysis.

¹⁸ If the patient is discharged before Visit 7, the resting SpO₂ is only required 1 time per day.

5.5.1.2 Screening

Screening will occur up to 72 hours prior to Visit 1 (Baseline). The aim of the screening is to collect necessary data to confirm the patient's eligibility and can be ongoing up the randomization of the patient at Visit 1. A signed informed consent form must be obtained from the patient prior to any study-related activities. However, HRCT scan results and laboratory results already available in medical records at the time of informed consent can be used to confirm eligibility, if collected within 72 hours. Please refer to Table 3 for the clinical and laboratory parameters to be collected during screening.

Patients who do not meet the criteria for participation in this study (screening failure) may not be rescreened.

5.5.1.3 Visit 1, Baseline (Day 1)

Once all inclusion and exclusion criteria have been reviewed and recorded, and the patient has been found eligible, the patient will be randomized into one of the treatment groups and the first dose of study drug will be administered accordingly (see Section 5.4.5). Please refer to Table 2 for other clinical and laboratory parameters to be collected during the visit.

During the treatment period (Days 1 to 15), clinical and laboratory assessments and procedures should preferably be performed before IMP administration.

5.5.1.4 Visits 2 to 5 (Days 4, 7, 10 and 13)

Please refer to Table 2 for the clinical and laboratory parameters to be collected during these visits. For study drug administration schedule, see Section 5.4.5.

Effort should be made to adhere to the schedule of assessment. However, a window of ± 1 day will be allowed for all assessments scheduled for Visits 2 to 5. This does not include IMP administration.

During the treatment period (Days 1 to 15), clinical and laboratory assessments and procedures should preferably be performed before IMP administration.

5.5.1.5 Visit 6 (Day 15)

Please refer to Table 2 for the clinical and laboratory parameters to be collected during these visits. For study drug administration schedule, see Section 5.4.5.

Effort should be made to adhere to the schedule of assessment. However, a visit window of ± 1 day will be allowed for Visit 6 (Day 15).

During the treatment period (Days 1 to 15), clinical and laboratory assessments and procedures should preferably be performed before IMP administration.

The primary endpoint will be evaluated at Visit 6 (Day 15).

5.5.1.6 Visit 7 (Day 28)

An early follow-up visit will be performed at Day 28.

Please refer to Table 2 Schedule of Events Table 2 for the clinical and laboratory parameters to be collected during this visit. If the patient is discharged from the hospital before this visit, efforts should be made to adhere to the visit window of ± 3 days.

5.5.1.7 Visits 8 and 9, Follow-up (Weeks 6 and 10)

These visits can be conducted either as a follow-up telephone call or in-person visit, if the patient is still hospitalized. Please refer to Table 2 for the clinical parameters to be collected during the visits.

A window of ± 5 days will be allowed for Visits 8 and 9.

5.5.2 Patient information and physical examination

5.5.2.1 Demographics

The patient's date of birth, gender, race and ethnicity will be collected at screening, and recorded in the CRF.

5.5.2.2 Medical and surgical history

Details of the patient's relevant medical and surgical history as judged by the Investigator will be collected at screening, and recorded in the CRF.

5.5.2.3 Prior medication

Details of the patient's relevant prior medication as judged by the Investigator will be collected at screening, and recorded in the CRF.

5.5.2.4 Physical examination

A general physical examination will be performed at screening and recorded in the CRF. The assessment will be reported as "normal" or "abnormal". Any abnormalities should be specified and recorded as medical history.

Body weight and height will be recorded as a part of the physical examination.

5.5.2.5 Symptom onset information

Date of symptom onset will be collected at screening, and recorded in the CRF. This data is collected to explore the time between symptom onset and start of treatment.

5.5.3 Efficacy assessments

5.5.3.1 Pulmonary function (primary efficacy assessment)

The date and time of the requirement for invasive mechanical ventilation and extracorporeal membrane oxygenation (ECMO) will be assessed at Visits 1 to 7, and recorded in the CRF.

5.5.3.2 MEWS score

Modified early warning system score (MEWS) will be assessed at Visit 1 (Day 1), Visit 6 (Day 15) and Visit 7 (Day 28) and recorded in the CRF.

5.5.3.3 SpO₂, PaO₂ and FiO₂

Resting peripheral capillary oxygen saturation (SpO₂) will be measured 3 times per day at Visits 1 to 7, and recorded in the CRF. For Visit 7, if the patient is discharged from the hospital prior to this visit, the SpO₂ will be performed only once at this visit.

The partial pressure of oxygen (PaO₂) and the fraction of inspired oxygen (FiO₂) will be measured at screening, at Visit 6 and Visit 7, and recorded in the CRF.

5.5.3.4 Hemogasanalysis

Hemogasanalysis will be assessed at Visits 1 to 7, and recorded in the CRF.

Analysis may for example include pH, carbon dioxide tension (pCO₂), oxygen tension (pO₂), electrolytes, lactate and hemoglobin.

5.5.3.5 Oxygen supplementation

Oxygen supplementation will be assessed at Visits 1 to 7. The date, time and amount of supplementation will be recorded in the CRF.

5.5.3.6 High-resolution computed tomography

A high-resolution computed tomography scan (HR-CT) of the chest or a chest X-ray will be performed at screening, Visit 6 (Day 15) and Visit 7 (Day 28). The HR-CT scan or the X-ray of the chest will be recorded in the CRF and reported as “normal” or “abnormal”.

Any abnormalities reported at screening should be specified and recorded as medical history.

5.5.3.7 Laboratory assessments

Blood samples for determination of the laboratory assessments described in Table 3 will be drawn at screening, and at Visits 1 to 7. The date and time of blood sampling will be recorded in the CRF.

Table 3 Laboratory assessments

<p><u>Biochemistry</u></p> <p>Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin (if >upper limit of normal also conjugated and non-conjugated bilirubin) Prothrombin Time/International Normalized Ratio (PT-INR) Fibrinogen Complement C3/C4 Cardiac troponin Creatinine C-reactive protein (CRP) Electrolytes (Sodium, Potassium, Calcium) Glucose</p>	<p><u>Hematology</u></p> <p>Hemoglobin Platelet count White blood cells RBC Differential blood count</p> <p><u>Hyperinflammatory parameters</u></p> <p>Ferritin LDH D-dimers</p> <p><u>Additional testing at screening</u></p> <p>TB screening PCR SARS-CoV-2</p>
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All laboratory samples will be analysed at the respective local hospital laboratory according to their standard routines.

The laboratory results will be entered by the respective hospital into the study eCRF.

5.5.3.7.1 Additional testing at screening

Patients randomized to study with no clinical suspicion of active or latent tuberculosis as per study exclusion criteria (see 5.3.2) may on rare occasions test positive for TB based on lab screening. Should such situation occur, the principal investigator will decide based on the assessed benefit/risk for the patient whether or not it is in the best interest of the patient to continue in the study.

For study sites where PCR is not part of hospital routine for confirming SARS-CoV-2 diagnosis/eligibility as per study inclusion criteria (see 5.3.1), PCR test results are accepted post randomization not to delay treatment. The test can be done in specimens of different origins as decided by principal investigator. Should an enrolled patient show a negative PCR test result for SARS-CoV-2, the principal investigator will decide based on the assessed benefit/risk for the patient whether or not it is in the best interest of the patient to continue in the study. Such patient is to be excluded from the study efficacy analysis but included in the safety analysis.

5.5.3.8 Survival and hospital discharge

Data on survival and hospital discharge will be collected at Visits 7 (Day 28), Visit 8 and 9 (Weeks 6 and 10) and recorded in the CRF.

5.5.4 Safety assessments

5.5.4.1 Adverse events

5.5.4.1.1 Definitions

Adverse event (AE)

An AE is any adverse change, i.e., any unfavorable and unintended sign, including an abnormal laboratory finding, symptom, or disease that occurs in a patient during the course of the study, whether or not considered by the investigator as related to study treatment.

A treatment-emergent AE is any AE temporally associated with the use of study treatment whether or not considered by the investigator as related to study treatment.

Adverse events include:

- Exacerbation of a pre-existing disease.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed during the course of the study even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at study start that worsen following the start of the study (i.e., signing of informed consent).
- Abnormal assessments, e.g., change on physical examination, ECG findings, if they represent a clinically significant finding that was not present at study start or worsened during the course of the study.
- Laboratory test abnormalities are considered as AEs if they represent a clinically significant finding, symptomatic or not, which was not present at study start or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study treatment. An AE is any untoward medical occurrence in a patient administered a pharmaceutical product; the event does not necessarily have a causal relationship with the treatment or usage.

5.5.4.1.2 Intensity of adverse events

The intensity of clinical AEs is graded on a three-point scale – mild, moderate, severe – and is reported on specific AE pages of the CRF.

If the intensity of an AE worsens during study treatment administration, only the worst intensity should be reported on the AE page. If the AE lessens in intensity, no change in the severity is required.

If the intensity of an AE with an onset date between informed consent signature and start of study treatment and which is ongoing at the start of treatment worsens after the start of study treatment, a new AE page must be completed. The onset date of this new AE corresponds to the date of worsening in intensity.

The three categories of intensity are defined as follows:

Mild

The event may be noticeable to the patient. It does not influence daily activities, and usually does not require intervention.

 Moderate

The event may make the patient uncomfortable. Performance of daily activities may be influenced, and intervention may be needed.

 Severe

The event may cause noticeable discomfort, and usually interferes with daily activities. The patient may not be able to continue in the study, and treatment or intervention is usually needed.

A mild, moderate, or severe AE may or may not be serious, see Section 5.5.4.2. These terms are used to describe the intensity of a specific event. Medical judgment should be used on a case-by-case basis.

Seriousness, rather than severity assessment, determines the regulatory reporting obligations.

5.5.4.1.3 Relationship to study treatment

Each AE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the study treatment, and reported as either related or unrelated. The determination of the likelihood that the study treatment caused the AE will be provided by an investigator who is a qualified physician.

5.5.4.2 Serious adverse events

5.5.4.2.1 Definitions of serious adverse events

An SAE is defined by the International Conference on Harmonisation (ICH) guidelines as any AE fulfilling at least one of the following criteria:

- Fatal.
- Life-threatening: refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe.
- Requiring inpatient hospitalization, or prolongation of existing hospitalization.
- Resulting in persistent or significant disability or incapacity.
- Congenital anomaly or birth defect.
- Medically significant: refers to important medical events that may not immediately result in death, be life-threatening, or require hospitalization but may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the patient, and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The following reasons for hospitalization are exempted from being reported:

- Hospitalization for cosmetic elective surgery, or social and/or convenience reasons.

- Hospitalization for pre-planned (i.e., planned prior to signing informed consent) surgery or standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a patient with stable angina pectoris.

However, complications that occur during hospitalization are AEs or SAEs (for example if a complication prolongs hospitalization).

5.5.4.3 Reporting requirement of adverse events

5.5.4.3.1 Reporting of adverse events

Irrespective of seriousness, the following adverse events are considered as adverse events of special interest and must be reported on AE page of the CRF.

In all patients:

- AEs leading to discontinuation of study treatment

Infusion related reactions including anaphylactic/anaphylactoid reactions. In patients treated with emapalumab, the following AEs will be considered of special interest:

- All new infections.

In patients treated with anakinra, the following AEs will be considered of special interest:

- Severe neutropenia defined as neutrophil count $< 0.5 \times 10^9/l$.

No other AEs are required to be reported on the AE page of the CRF

5.5.4.3.2 Reporting of serious adverse events

All SAEs occurring after study drug initiation and up to the end of study visit (Visit 9, Week 10) must be reported on AE pages in the CRF and on an SAE form, regardless of the investigator-attributed causal relationship with study treatment.

Abnormal laboratory findings

Abnormal laboratory findings, if serious, must be reported on specific AE pages of the CRF.

Following laboratory variables are collected for the assessment of efficacy (see Section 6.5.3.2) at screening and during the treatment period, and are not required to be reported as SAEs as described above: WBC including differential counts, RBC, Hgb, platelet count, fibrinogen, complement C3/C4, PT-INR, and cardiac troponin; ALT, AST, total bilirubin, creatinine, ferritin, LDH, D-dimer, CRP, electrolytes (sodium, potassium, calcium), and glucose.

5.5.4.3.3 Follow-up of serious adverse events

Serious adverse events still ongoing at the end of study visit (Visit 9, Week 10) must be followed up until resolution or stabilization, or until a definite event outcome is provided, e.g., resolved with sequelae or death.

5.5.4.3.4 Reporting procedures

All SAEs must be reported by the investigator to the Sobi drug safety department within 24 hours of the investigator's first knowledge of the event.

All SAEs must be recorded on an SAE form, irrespective of the study treatment received by the patient, and whether or not this event is considered by the investigator to be related to study treatment.

The SAE forms must be e-mailed to the Sobi drug safety department:

- NI-0501drugsafety@sobi.com

The investigator must complete the SAE form in English, and must assess the causal relationship of the event to study treatment.

Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. The Sobi drug safety department may contact the investigator to obtain further information.

If the patient is hospitalized in a hospital other than the study site, it is the investigator's responsibility to contact this hospital to obtain all SAE relevant information and documentation.

The reference safety document to assess expectedness of a suspected serious adverse reaction and for reporting by the Sponsor to Health Authorities, IRBs/IECs, and investigators is:

- For emapalumab - the reference safety information section of the Investigator's Brochure [Emapalumab IB].
- For anakinra - Section 4.8. of anakinra SmPC (Kineret SmPC) + i.v. data

5.5.4.4 Pregnancy

5.5.4.4.1 Reporting of pregnancy

Irrespective of the treatment received by the patient, any pregnancy occurring after study drug initiation up to the end of study visit (Visit 9, Week 10) must be reported within 24 hours of the investigator's knowledge of the event. Pregnancies of female patients will be followed until final outcome of pregnancy. For emapalumab treated patients; Pregnancies of a female partner of male patients in the study need to be similarly reported and to be followed until the final outcome of the pregnancy

Pregnancies must be reported on the pregnancy form which is e-mailed to the Sobi drug safety department (NI-0501drugsafety@sobi.com), and on an AE page in the CRF.

5.5.4.4.2 Follow-up of pregnancy

Any pregnancy must be followed to its conclusion and its outcome must be reported to the Sobi drug safety department. This information will be only entered in the drug safety database.

Any AE associated with the pregnancy occurring during the study must be reported on separate AE pages in the CRF. Any SAE occurring during the pregnancy must be reported on an SAE form as described in Section 5.5.4.3.

5.5.4.5 Laboratory safety assessments

For details on laboratory assessments, see Section 5.5.3.7.

5.5.4.6 Vital signs

Vital signs (body temperature, blood pressure, heart rate, respiratory rate and oxygen saturation) will be measured at screening, and Visit 1 to 7, and recorded in the CRF.

For AE reporting of abnormalities, see Section 5.5.4.3.

5.5.4.7 Electrocardiograms

A 12-lead ECG recording will be performed at screening, Visit 6 (Day 15) and Visit 7 (Day 28), and recorded in the CRF. The ECG assessments will be performed at site and will be reported as “normal” or “abnormal”. Any abnormalities should be specified. Abnormalities reported at screening should be recorded as medical history.

For AE reporting of abnormalities, see Section 5.5.4.3.

5.5.4.8 Pregnancy Test

Female of childbearing potential will have a urine pregnancy test taken at screening and at Visit 6 (Day 15). The outcome of the test will be reported as “positive” or “negative” in the CRF.

5.5.4.9 Immunogenicity

Immunogenicity samples will be collected for all patients receiving active study treatment at Visit 1 Pre-dose, at Visit 6 at end-of infusion (for anakinra a sample should be taken after the first infusion per day) at Visit 7. If the patient is coming to the clinic at the follow-up visits, immunogenicity samples will also be collected at Visit 8 and Visit 9. The date and time of blood sampling will be recorded in the CRF. Samples will be sent to central laboratory for analysis.

5.5.4.10 Viral shedding

Samples for viral shedding will be collected for all patients at Visits 1, 4, 6 (Day 15) and 7 (Day 28). For patients coming to the clinic for the follow-up visit, samples will also be collected at Visit 8 and Visit 9. The date of the sampling will be recorded in the CRF. Samples will be sent to a central laboratory for analysis.

5.5.4.11 Data Review Committee

The Data Review Committee members are to be independent from any of the sponsors and without any conflicts of interest, providing their expertise in intensive care, inflammation, infectious diseases and will be involved in study oversight, safety monitoring and interpretation of the emerging study results.

5.5.4.12 Safety Review Committee

An SRC consisting of internal Sobi members (voting) and coordinating investigators (non-voting) members is established to monitor study participant safety in the study. Clinical study safety information (eg AEs, SAEs, laboratory values, ECGs, vital signs, and additional safety related study assessments, as required) is monitored and reviewed on a continuous basis by SRC from study start to database lock.

If two patients develops a life threatening or fatal adverse event suspected to be study drug related then an ad hoc SRC meeting will be held within 24 hours after the Sponsor awareness of the Event. At this meeting the decision on continuation of the study with or without changes or to halt the enrollment of the specific study arm will be taken. Details are described in a separate written operating procedures for the SRC.

5.5.4.13 Specific safety monitoring and management during the study

Infusion related reactions for all treatment arms:

The infusion related reactions will be closely monitored by the treating physician. Should severe allergic reactions (such as anaphylactic shock) occur, the patient would be managed according to the local standard treatment guidelines.

Anakinra treatment:

- Neutrophil counts should be assessed prior to initiating and during anakinra treatment. Should neutropenia (neutrophil count $< 1.0 \times 10^9/L$) occur in a patient treated with anakinra, dose reduction or discontinuation of the treatment may be considered as judged by the investigator. Should neutropenia (neutrophil count $< 0.5 \times 10^9/L$) occur in a patient treated with anakinra, the treatment should be discontinued.
- Anakinra is mainly eliminated by the kidney. Should severe renal impairment ($CL_{Cr} < 30$ ml/min) or end stage renal disease occur, the reduction of anakinra dose (100mg IV 2 times daily) should be considered as judged by the investigator.

Emapalumab treatment:

- Monitoring of new infections is requested throughout the study. Type of investigation, specimen, result and pathogen identified will be captured in the CRF. Such data will be captured for all new infection. Should serious infection caused by pathogens potentially favored by $IFN\gamma$ neutralization, i.e. mycobacteria, histoplasma capsulatum, herpes zoster, salmonella and shigella occur in a patient treated with emapalumab, the treatment should be stopped, and appropriate anti-infective treatment should be initiated.

5.5.5 Exploratory assessments

5.5.5.1 Clinical Status

Data on clinical status based on a 7-point ordinal scale will be collected at Visits 1 to 9 and recorded in the CRF.

The scale consists of the following categories:

1. Death
2. Hospitalized, requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
3. Hospitalized, requiring non-invasive ventilation or high flow oxygen devices
4. Hospitalized, requiring supplemental oxygen
5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care
6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care
7. Not hospitalized

5.5.5.2 Pharmacokinetics

PK blood samples will be collected for all patients receiving active study treatment. At Visit 1 sampling should be done pre-dose and at end-of infusion and during Visits 2, 3, 4, 5 and 6 a PK sample should be taken at end-of infusion. For anakinra treated patients; samples will only be collected in connection with the first infusion per day. In addition, for emapalumab treated patients, a PK sample will be collected also at Visit 7 (Day 28) and during follow-up on Visit 8 and 9 in case the patient is at the clinic for these visits. It should be noted that a separate iv line will have to be used when collecting the PK samples, ie not the same iv line as used for the iv infusion of active study treatment.

The date and time of blood sampling will be recorded in the CRF. Samples will be sent to a central laboratory for analysis.

5.5.5.3 Pharmacodynamics

Blood samples for determination of CXCL9, IFN γ , IL-1, IL-6, sIL-2R and selected exploratory parameters will be collected at Visit 1 to 9 at the end of infusion (for anakinra treated patients; samples will only be collected in connection with the first infusion per day). The date and time of blood sampling will be recorded in the CRF. It should be noted that a separate iv line will have to be used when collecting the PD samples, ie not the same iv line as used for the iv infusion of active study treatment.

Samples will be sent to a central laboratory for analysis.

6 Quality control and quality assurance

This study will be conducted in compliance with this protocol, study specific procedures, CRO SOPs, Sobi SOPs, the ICH Guideline for GCP [1], and applicable regulatory requirements.

The Sponsor/CRO will establish a systematic, prioritized, risk-based approach to monitoring and, considering the current situation, will need to utilize remote monitoring. The Sponsor/CRO will develop a risk management plan with the aim to limit the contacts with patients and site personnel during the emergency period, while ensuring the patients safety and integrity, compliance with the protocol, study specific procedures and applicable regulatory requirements.

To ensure ongoing patient safety and well-being, and control risks to study critical processes, such as review of all informed consent forms and all primary efficacy variables, alternative mechanisms of oversight will be introduced (such as phone calls, video calls, remote monitoring etc). The Sponsor/CRO will also investigate if other measures for sharing data can be implemented, e.g. sharing de-identified source documents in shared drives/locations.

On-site monitoring visits will be postponed until the emergency period is over. Source documents will then be reviewed for verification of agreement with data in CRFs.

The investigator or institution guarantees access to source documents by Sobi, its representatives, and appropriate regulatory agencies.

The study site may be subject to a quality assurance audit by Sobi or its representatives, as well as inspection by appropriate regulatory agencies.

It is important that the investigator(s) and the(ir) relevant personnel are available during the monitoring visits and possible audits and that sufficient time is devoted to the process.

7 Statistical plan

7.1 Determination of sample size

The study will enroll a total of 54 patients, 18 per arm according to the 1:1:1 randomization.

The sample size has been estimated based on the following assumptions:

- An overall one-sided significance level for efficacy of 0.097 (9.7%) and a power of 74% for each comparison under the assumption that the true success rates are 50% in the SoC group increasing to 80% in the emapalumab or anakinra groups.
- The study will consist of two stages, with equal numbers of patients randomised into Stage 1 and into Stage 2 per treatment arm.
- There is the potential to stop for futility or for efficacy of emapalumab or anakinra (or both) at the end of Stage 1, but only the futility rule is binding and irrespective of the Stage 1 results, the study will not be stopped for efficacy but continue to accrue safety data.

More specifically:

- The emapalumab or anakinra arm (or both) will be stopped at the end of Stage 1 for futility if the one-sided p-value in favour of emapalumab/anakinra is > 0.690 .

- Efficacy of the emapalumab or anakinra arm (or both) will be declared at the end of Stage 1 if the one-sided p-value in favour of emapalumab/anakinra is < 0.025 .
- If the trial continues to Stage 2, efficacy will be declared at the end of Stage 2 if the one-sided p-value in favour of emapalumab/anakinra is < 0.159 .

The calculations on the operating characteristics of this design have been undertaken using PASS, Version 14: Group-Sequential Tests for Two Proportions (Simulation).

The value for the type I error has been chosen in recognition of the urgent unmet medical need to allow the identification of a signal, at least, from a statistical perspective. Having seen a statistical signal, it is then a matter of evaluating whether the observed treatment differences represent clinically relevant effects that can satisfy that unmet need.

Assuming no untoward safety signal is observed and no futility stopping occurs at the Stage 1 interim, the decision may be taken to increase the sample size beyond 54 patients in order to accrue further safety and efficacy data. Details of this would be described in a protocol amendment.

In case the outcome is statistically convincing, i.e. statistically significant on a 5% level in the stage 2 analysis, efficacy will be considered confirmed and the results may, where warranted, be used to seek regulatory approvals.

7.2 Definition of study populations

All efficacy analyses will be conducted on the modified intention-to-treat (mITT) population which will comprise all randomized patients except patients who did not receive study treatment or patients who tested negative to SARS-CoV-2 diagnosis confirmation by PCR testing.

In case of exclusion due to tested negative to SARS-CoV-2 diagnosis confirmation by PCR testing, additional patients may be recruited to ensure an adequate number of evaluable patients for the efficacy analysis.

The Safety population will comprise all patients who received at least one dose of study treatment or standard of care.

Patients will be included in the groups to which they were randomized for all evaluations of efficacy and in the groups according to treatment received for all evaluations of safety.

7.3 Overall statistical and analytical plan

Statistical analysis will be performed using SAS software Version 9.4 or later (SAS Institute, Inc, Cary, North Carolina, United States).

7.3.1 General statistical issues

This design has acceptable properties in terms of the false positive potential, controlling the overall type I error at 9.7%, for each of the two treatment comparisons.

Secondary endpoints will be evaluated in a descriptive way. In some cases p-value comparisons will be undertaken, but these are to be interpreted in an exploratory way.

7.3.2 Demographics and baseline characteristics

Demographic and baseline characteristics will be summarized in appropriate tabular presentations.

For measurements of continuous endpoints, summary statistics will include n, mean, median, standard deviation, minimum and maximum values. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented.

7.3.3 Analysis related to primary objective

7.3.3.1 Primary endpoint

7.3.3.1.1 Treatment success

For the analysis of the primary endpoint, each of the pairwise comparisons, emapalumab/anakinra versus standard of care, at both the end of Stage 1 and at the end of Stage 2, will be undertaken using Fishers Exact test comparing the proportion of patients with treatment success. This will be supplemented by the presentation of one-sided exact confidence intervals of the differences in proportion between emapalumab/anakinra and standard of care, with confidence coefficients of 97.5% at the end of Stage 1 and 84% at the end of Stage 2. Two-sided confidence intervals of the proportions in each group will also be presented, using the method of Clopper-Pearson [18].

The primary analysis will not adjust for the stratification factor glucocorticoid use at inclusion due to the small sample size at Stage 1. However, a sensitivity analysis of the primary endpoint using exact logistic regression will be performed at Stage 1 and 2. This will allow for conditional testing of the treatment effect given the stratification factor. The results of the analysis will be presented in terms of model-adjusted treatment success rates for each treatment group, and p-values and confidence intervals for the odds ratio of the pairwise comparisons to the standard-of-care arm.

7.3.3.2 Secondary endpoints supporting the primary objective

7.3.3.2.1 Time to mechanical ventilation and overall survival

Analysis of the time to mechanical ventilation from the point of randomization will be undertaken by plotting Kaplan-Meier curves for each of the 3 treatment groups and by pairwise comparisons (emapalumab/anakinra versus standard of care) using the logrank test. Hazard ratios will be estimated using the Cox proportional hazards model and these will be presented together with 90% two-sided confidence intervals.

Overall survival (time to death from the point of randomization) and time to hospital discharge (from the point of randomization) will not be analysed at the end of Stage 2, but at the end of the follow-up period. This endpoint will be analysed as for time to mechanical ventilation.

7.3.3.2.2 Change from baseline in MEWs score

Change from baseline in MEWs score at Day 15 will be analysed using analysis of covariance (ANCOVA) including treatment arm as a fixed factor and baseline MEWs score as a covariate. Least square mean change per group, associated 90% two-sided CI, and p-values for the comparison vs. standard of care, will be presented.

7.3.3.2.3 Change from baseline in hyperinflammatory parameters

Change from baseline during treatment until Day 15 with measurements performed every 3 days of the following parameters will be summarized using descriptive statistics:

- Ferritin
- LDH
- D-dimers

7.3.3.2.4 Change from baseline in other relevant laboratory parameters

Change from baseline during treatment until Day 15 with measurements performed every 3 days of the following parameters will be summarized using descriptive statistics:

- WBC with differential counts
- RBC
- Hb
- Platelet count
- Fibrinogen
- Complement C3/C4
- Prothrombin Time
- Cardiac troponin
- Liver tests (AST, ALT, total bilirubin levels)
- CRP
- Creatinine
- Electrolytes (Sodium, Potassium, Calcium)
- Glucose

7.3.3.2.5 Change from baseline in resting SpO₂ and oxygen supplementation

Change from baseline during treatment until Day 15 with measurements performed every 3 days will be summarized using descriptive statistics for each of these parameters.

7.3.3.2.6 Change from baseline in PaO₂/FiO₂

Change from baseline (screening) during treatment until Day 15 will be summarized using descriptive statistics.

7.3.3.2.7 Change from baseline in hemogasanalysis

Change from baseline during treatment until Day 15 with measurements performed every 3 days will be summarized using descriptive statistics for each of the collected parameters.

7.3.4 Analysis related to secondary objective

7.3.4.1 Adverse events

Reported AEs during the study will be coded using MedDRA. The incidence of AEs will be summarized in frequency tables by treatment, system organ class, preferred term and maximum severity. Separate tabulations will be performed for serious and non-serious AEs.

7.3.4.2 Anti-drug antibodies

The number and percentage of patients with ADA and NAb at baseline and at each post-baseline assessment will be summarized.

7.3.5 Analysis related to the exploratory objective

Clinical status using the 7-point ordinal scale is an exploratory endpoint and the data collected will be summarized to show the number and percentage of patients in each category over time.

PK and PD data will be listed and summarized at each visit with descriptive statistics.

7.3.6 Interim analysis

The study will consist of one interim analysis (Stage 1) and a final analysis (Stage 2), with approximately the same numbers of patients randomised into Stage 1 and into Stage 2 per treatment arm. The Stage 1 interim analysis will be conducted after the accrual of at least 9 patients per treatment arm. See Section 7.1 for further details concerning the interim analysis.

7.3.7 Multiple comparison/multiplicity

There will be no adjustments for multiplicity for the two pairwise treatment comparisons for the primary endpoint. Multiplicity for the sequential comparisons at the end of Stage 1 and at the end of Stage 2 are however accounted for by the design.

7.3.8 Handling of missing data

There will be no imputation of missing data for the primary endpoint (treatment success by Day 15), but patients who discontinue study treatment (or discontinue the study if randomized to standard of care) prior to Day 15 and had IMV or ECMO on their last assessment by the time of study treatment discontinuation, will be considered not having achieved treatment success by Day 15. Patients discontinuing prior to Day 15 without ever having initiated IMV/ECMO, will be considered having achieved treatment success by Day 15. Patients discontinuing prior to Day 15 due to having significantly improved will be considered having achieved treatment success. Patients who died by Day 15, have not achieved treatment success regardless of IMV/ECMO use by Day 15.

For change-from-baseline efficacy endpoints at Day 15, the last observation carried forward (LOCF) approach will be used to impute missing data, using the last post-baseline observation available for each patient.

8 Data collection, handling and record keeping

8.1 Data standards

Collection of data should be performed in the CDASH format, according to the CDISC. The standards should be used to the extent possible and/or required for the specific study/project. The minimum requirement of the CDISC standard is to collect all core variables specified as 'Required' in the Study Data Tabulation Model format.

8.2 Case report form

A CRF is required and should be completed for each included patient. In this study an electronic CRF will be used. The completed original CRFs are the sole property of Sobi and should not be made available in any form to third parties, except for authorized representatives of appropriate Regulatory Authorities, without written permission from Sobi.

It is the responsibility of the investigator to ensure completion and to review and approve all CRFs. CRFs must be signed electronically by the investigator. These signatures serve to attest that the information contained on these CRFs is correct. At all times, the investigator has final responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs.

8.3 Source data

Patient source documents are the patient's medical records maintained at the study site. In most cases, the source documents will be the hospital's or the physician's chart, including laboratory

test results, radiology results, ECG etc. In those cases, the information collected in the CRFs must match those charts.

A separate source document location agreement will be completed and signed by the Principal Investigator and the site monitor.

Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g. via an audit trail).

8.4 Protocol deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of patients. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to study patients.

A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

When a deviation from the protocol is identified, the investigator or designee must ensure Sobi/CRO is notified. Sobi/CRO will follow up with the investigator, as applicable, to assess the deviation and the possible impact to the safety and / or efficacy of the patient to determine patient continuation in the study.

The investigator and CRO must contact Sobi immediately if a deviation is discovered that significantly affects or has the potential to significantly affect human subject protection or the reliability of study results.

The investigator will also assure that deviations are reported and documented in accordance with IEC and applicable regulatory requirements.

8.5 Database closure

Prior to database closure, all tasks or criteria defined in the data management plan must be completed and documented. The study database must be locked before generation of any results. The database lock will be approved by relevant study personnel and all edit accesses will be removed. Following database closure, the study database can only be unlocked in case critical errors, affecting the main conclusions of the study, are discovered.

8.6 Record retention

The investigator should maintain a record of the location(s) of investigator's essential documents as defined in the ICH GCP Guideline [1] including source documents and should have control of

and continuous access to all essential documents and records generated by the investigator/institution before, during, and after the study.

All documents and data relating to the study will be kept securely by the investigator in a secure file and/or electronically. The storage system used during the study and for archiving (irrespective of the type of media used) should provide for document identification, version history, search and retrieval. The data will be available for evaluation and/or audits from Health Authorities, Sobi or Sobi's representatives.

When a copy is used to replace an original document (e.g. source documents, CRF), the copy should fulfill the requirements for certified copy as defined in ICH GCP Guideline [1].

The records should be retained by the Investigator as specified in the Clinical Trial Agreement and in accordance with local regulations.

If the investigator relocates, retires, or for any reason withdraws from the study, the study records may be transferred to an acceptable designee, such as another investigator or another institution. Archiving on behalf of the investigator can also be delegated to Sobi.

9 End of study

The end of this study is defined as the date of the last patient's last visit/end of study call (Visit 9, Week 10).

10 Sponsor's discontinuation criteria

Sobi reserves the right to discontinue the study prior to inclusion of the intended number of patients, but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the investigator must contact all participating patients within 30 days. All study materials must be collected and all the CRFs completed to the greatest extent possible.

11 Dissemination and publication of results

Sobi will register the study by posting study information and post study results regardless of outcome on a publicly accessible website in accordance with applicable laws and regulations, e.g., on www.clinicaltrials.gov and [EudraCT](http://eudract.europa.eu). The results of this study will be published within 12 months of the end of study.

Sobi is committed to publishing study results in a complete, accurate, balanced, transparent and timely manner. Sobi follows the principles of the International Committee of Medical Journal Editors (ICMJE) recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals including criteria for authorship [3].

The data from this study will be considered for reporting at a scientific meeting or for publication in a scientific journal. The Sponsor will be responsible for these activities and will

work with the investigators to determine how the publication is written, the number and order of authors, the journal or scientific meeting to which it will be submitted, and other related issues. The results of the study, or any part thereof, shall not be published without the prior written consent and approval of Sobi, such consent and approval not to be unreasonably withheld.

12 Reference list

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 - 17 Eloseily EM et al. Benefit of anakinra in treating pediatric secondary hemophagocytic lymphohistiocytosis. *Arthritis Rheumatol*. 2020;72:326-334 doi: 10.1002/art.41103
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Sobi

Emapalumab/Anakinra

Clinical Study No: Sobi.IMMUNO-101

Appendix 1

Additional Protocol Signatures

Sponsor's Clinical Program Leader

Karin Becker, MSc Pharm
Clinical Program Leader
E-mail: karin.becker@sobi.com

DocuSigned by:
Karin Becker

 Signer Name: Karin Becker
Signing Reason: Jag godkänner dokumentet
Signing Time: 30 June 2020 | 12:11:11 CEST

Signature  C55B3FC6C36A49F3BC526D2C1141F604

30 June 2020 | 12:11:15 CEST

Date

Sponsor's Statistician

Henrik Andersson, MSc
Statistician
E-mail: henrik.andersson@sobi.com

DocuSigned by:
Henrik Andersson

 Signer Name: Henrik Andersson
Signing Reason: Jag godkänner dokumentet
Signing Time: 30 juni 2020 | 02:14:18 PDT

Signature  40F3D60C048844FEB4B1AFE3D0BEEF64

30 juni 2020 | 02:14:22 PDT

Date

Appendix 2**Study Administrative Structure**

Sponsor:	Swedish Orphan Biovitrum AB (publ), SE-112 76 Stockholm, Sweden Phone: +46 8 697 20 00
Study sites:	12 to 20 study sites in Italy and US.
Monitoring:	Pharmaceutical Research Associates, Inc., Raleigh, North Carolina, USA (CRO)
SAE reporting:	Swedish Orphan Biovitrum AB (publ).
Data management:	Pharmaceutical Research Associates, Inc., Raleigh, North Carolina, USA (CRO)
Statistics:	Swedish Orphan Biovitrum AB (publ).
Investigational products (production):	See Section 5.4.2.
Investigational products (packaging and labeling):	Rechon Life Science AB (Limhamn, Sweden).
Clinical laboratory:	All clinical laboratory safety assessments will be performed at the local hospital.
Central laboratory	Emapalumab PK samples: Sobi AG, Plan-les-Ouates, Switzerland Exploratory biomarkers: Sobi AG, Plan-les-Ouates, Switzerland Emapalumab ADA samples: LGC, Cambridgeshire, United Kingdom Viral shedding: A central lab to be confirmed. Anakinra PK & ADA samples: York Bioanalytical Solutions Limited, York, United Kingdom Anakinra Nab samples: Wieslab AB, Malmö, Sweden

Appendix 3**Exemption Letter Italy**

AIFA
Italian Medicines Agency
Via del Tritone, 181
I-00187 Roma
Italy

March 16, 2020

Dear Sirs,

Re: Clinical trial of emapalumab and anakinra in patients with Coronavirus disease (COVID-19)

Swedish Orphan Biovitrum AB is planning to conduct a clinical trial with emapalumab and Kineret (anakinra) in patients with Coronavirus disease (COVID-19) and hyperinflammation.

The protocol (Sobi.IMMUNO-101, EudraCT **2020-001167-93**) has been prepared in response to the request from the President of the Italian Consiglio Superiore di Sanità, Prof. Franco Locatelli, and the Scientific Director of the National Institute for Infectious Diseases (Ospedale Lazzaro Spallanzani, coordinating site for the COVID-19 pandemic in Italy), Prof. Giuseppe Ippolito.

It will be a randomised open study with three parallel arms, emapalumab or anakinra as add-on therapy to Standard of Care, to be compared to Standard of Care only. The study will comprise up to 54 patients and cover a treatment duration of 2 weeks. The assessment will follow a step-wise approach which will be described in the protocol.

The CTA includes:

1. The CTA Form
2. The Clinical Study Protocol
3. The Patient Information and Informed Consent
4. The already existing IB for emapalumab (supporting HLH indications)
5. SmPC for Kineret, USPI for emapalumab
6. The labelling of the IMPs

The clinical trial will be submitted for review by the Ethics Committee.

It should be noted that due to the urgency of the situation, the Sponsor has for this protocol requested exemptions to what is required for a Clinical Trial Application and when conducting a clinical trial:

1. An IMPD has not been established. However, Kineret is approved centrally in the EU/EEA since March 2002 (SmPC enclosed). Emapalumab was approved by the FDA for primary hemophagocytic lymphohistiocytosis (pHLH) in November 2018 (USPI enclosed). Further, clinical trials with emapalumab to document the pHLH indication (Protocols NI-0501-04, -05 & -09) have previously been approved in Italy. The batch planned for the current study is the same which was used for Protocols NI-0501-04, -05 in Italy, with the study specific labelling adjusted.

Please note that for emapalumab, the same IMPD will be used as for study NI-0501-09 (NI-0501 IMPD Part 3 – November 2017). The QP certification site will be ABF Pharmaceutical Services GmbH, Gastgebasse 5-13, 1230 Vienna, Austria or Swedish Orphan Biovitrum AB (publ), the latter being an addition in comparison to the IMPD. The packaging site will be ABF or Rechon, PO Box 60043, Soldattorpsvägen 5, SE-216 10 Limhamn Sweden, the latter also being an addition in comparison to the IMPD.

2. Contract negotiations with hospitals is a time consuming process and it will not be possible to finalise this in time for start of the study. The principal investigators at each site will however be required to sign the Clinical Study Protocol.
3. SAEs and AEs will be collected according to instructions in the protocol, in short:
 1. All fatal and life-threatening SAEs occurring after study drug (emapalumab, anakinra) initiation or after randomisation to Standard of Care must be reported on an SAE form to the company and on AE pages in the CRF.
 2. Non-serious AEs *of special interest*, as defined in the protocol, will be recorded only in the CRF.
 3. Abnormal laboratory findings, if serious (fatal or life-threatening), must be reported on an SAE form to the company and on AE pages in the CRF. Certain lab values are however not required to be reported as SAEs as defined in the protocol.

We will follow Directive 2001/20/EC, Article 17 1(a) and shall ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening will be reported to competent authorities and to the concerned Ethical

Committees within seven days. We will not be able to comply with Article 17(b) for all other suspected serious unexpected adverse reactions to be reported within fifteen days since they will not be collected.

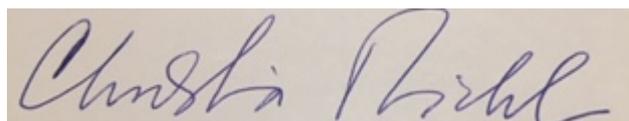
Based on the known safety profile of emapalumab and Kineret, the sponsor is of the opinion that their administration in the unapproved indication of COVID-19 infection would not pose additional risk to subject safety compared to normal clinical practice.

4. The Sponsor will establish a risk-based approach to monitoring and, considering the current situation, will need to utilize remote monitoring only during study conduct.

To ensure ongoing subject safety and well-being, and control risks to study critical processes, such as review of informed consent forms and primary efficacy variables, alternative mechanisms of oversight will be introduced (such as phone calls, video calls etc). The Sponsor will also investigate if other measures for sharing data can be implemented, e.g. sharing de-identified source documents in shared drives/locations.

5. CV:s for the principal investigator at each site will be collected, but not for the subinvestigators.
6. Information on experience of prior clinical trials and GCP training for the investigators will not be collected.
7. Financial disclosure forms for the investigators will not be collected.
8. Delegation log on site will not be implemented.
9. A source data documentation log will not be established
10. A sample handling procedure will not be provided.
11. Laboratory accreditation will not be available at start of the study but collected later.

Looking forward to any comments AIFA may have. Yours sincerely,



Sobi

Emapalumab/Anakinra

Clinical Study No: Sobi.IMMUNO-101

Christina Rickhammar

VP Global Regulatory Affairs

Swedish Orphan Biovitrum AB (publ)